February 14, 2001

Mr. James Cooper
Executive Director
SOCMA Sulfosuccinates Group
1850 M Street, NW
Suite 700
Washington, D.C. 20036

Dear Mr. Cooper:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for Sulfosuccinates, posted on the ChemRTK Web Site on, September 14, 2001. I commend the SOCMA Sulfosuccinates Group (SSG) for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Chemical RTK HPV Challenge Program website EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

Of the three chemicals, sodium di(2-ethylhexyl) sulfosuccinate is listed as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA). FDA publicly available files may contain toxicity data to support these claims.

As with other submissions where the available data are either inadequate or insufficiently documented, this case will remain open until adequate documentation is in hand.

EPA will post this letter and the attached Comments on the Chemical RTK web site within the next few days. As noted in the comments, we ask that SSG advise the Agency, within 60 days of the posting on the Chemical RTK website, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit general questions about the HPV Challenge Program through the Chemical RTK web site comment button or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@.epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Attachment

cc: W. Sanders
A. Abramson
C. Auer
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
SULFOSUCCINATES CATEGORY

SUMMARY OF EPA COMMENTS

The sponsor, The SOCMA Sulfosuccinates Group (SSG) of the Synthetic Organic Chemical Manufacturers Association (SOCMA), submitted a test plan and robust summaries to EPA for the sulfosuccinates category dated July 26, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on September 14, 2001. The sulfosuccinates category consists of sodium di(2-ethylhexyl) sulfosuccinate (CAS No. 577-11-7), sodium bis(1,3-dimethylbutyl) sulfosuccinate (CAS No. 2373-38-8), and sodium dicyclohexyl sulfosuccinate (CAS No. 23386-52-9).

EPA has reviewed this submission and reached the following conclusions:

1. Category justification. The grouping of the three sulfosuccinates into one category may be appropriate based on their structural similarities, physicochemical properties, and toxicological properties. However, the limited toxicity and toxicokinetic data presented for sodium bis(1,3-dimethyl-butyl) sulfosuccinate and sodium dicyclohexyl sulfosuccinate do not permit an adequate evaluation of this category approach for some health effects endpoints. The submitter needs to clearly state the toxicological similarities considered and address the issue of metabolism in the justification of their conclusion for not conducting additional testing.

2. Physicochemical and Environmental Fate Data. The submitter needs to provide measured melting point data for all three chemicals and stability in water data for at least one of these chemicals. In addition, the submitter needs to correct the EPIWIN calculations of the physicochemical and environmental fate values reported for sodium di(2-ethylhexyl) sulfosuccinate and sodium bis(1,3-di-methylbutyl) sulfosuccinate (See Test Plan comments below).

3. Health Endpoints. The submitter needs to provide additional information on toxicological and metabolic similarities of these chemicals to justify extrapolating genetic toxicity and developmental toxicity data on sodium di(2-ethylhexyl) sulfosuccinate to the other chemicals or conduct these studies on one of them to characterize these endpoints.

4. Ecotoxicity. EPA recommends an algal toxicity study on sodium di(2-ethylhexyl) sulfosuccinate because this chemical is the most lipophilic, is an anchor for the category, and showed significant toxicity to fish and daphnid. In addition, the submitter needs to provide test chemical purity information in study summaries (see specific comments on robust summaries).

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON SULFOSUCCINATES CATEGORY HPV CHALLENGE SUBMISSION

General Comments

Some robust summaries lack critical information and required data elements. EPA has provided specific comments on how to enhance the robust summaries to the standard established in EPA's HPV Challenge Program Guidance (http://www.epa.gov/chemrtk/guidocs.htm).
EPA reserves judgment on the adequacy of these studies pending submission of missing data elements (see specific comments on robust summaries)

Category Definition

The sulfosuccinates category contains three esters of sulfosuccinic acid. All three compounds share a sulfosuccinate backbone and alcohol moieties having either branched or cyclic alkyl groups with carbon numbers of either C_6 or C_8. These compounds are sodium di(2-ethylhexyl) sulfosuccinate, sodium bis-(1,3-dimethylbutyl) sulfosuccinate, and sodium dicyclohexyl sulfosuccinate.

Category Justification

The overall pattern seen with these compounds is that the C_6 members have higher water solubilities and lower octanol-water partition coefficients, bioconcentration factors, and aquatic toxicities than the C_8 member. Other values presented in the test plan also support the anticipated patterns including stability in water and biodegradation rates. Therefore, the submitter's assessment that the structural similarities of these compounds will be reflected in physicochemical properties is supported by the available experimental data.

The ecotoxicity data for this category of chemicals also support the grouping of these chemicals. A general pattern of increasing toxicity with ester carbon number is seen in the adequate tests for fish (for sodium bis(1,3-dimethylbutyl) sulfosuccinate and sodium di(2-ethylhexyl) sulfosuccinate) and daphnia (for sodium dicyclohexyl sulfosuccinate and sodium di(2-ethylhexyl) sulfosuccinate). Algal data are available only for sodium dicyclohexyl sulfosuccinate, and thus no comparison can be made.

The health effects data provided by the submitter for acute toxicity, repeated-dose toxicity, and reproductive toxicity also support the conclusion of similar toxicological properties for those endpoints. The developmental toxicity data for sodium di(2-ethylhexyl) sulfosuccinate showing fetal malformations cannot be directly extrapolated to the other two category chemicals because 2-ethylhexanol—a metabolite of sodium di(2-ethylhexyl) sulfosuccinate and a known developmental toxicant—will not be formed by the other two chemicals. Information on absorption, metabolism, and excretion is not available for the other category members. Therefore, the submitter needs to discuss the likely effects of the three different ester structures–-1-substituted vs 2-substituted vs cyclic–on metabolism and toxicity.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient)
Environmental Fate (Photodegradation, Stability in Water, Biodegradation, Fugacity)

The submitter needs to provide measured melting point data for these chemicals. In addition, the submitter needs to provide measured data for stability in water for at least one of the chemicals of this category to confirm estimated results. This would provide a more accurate picture on the stability in water of these chemicals. Please note that EPA recommends that measured physicochemical property and environmental fate data be provided to obtain more accurate input values for transport-distribution modeling. The use of estimated values introduces uncertainties that become magnified in modeling applications.

In addition, the submitter needs to correct the physicochemical and environmental fate values for sodium di(2-ethylhexyl) sulfosuccinate and sodium bis(1,3-dimethylbutyl) sulfosuccinate calculated using the EPIWIN. The EPIWIN values calculated by the submitter for these two chemicals are for the free acids and not for the sodium salts. It appears that the SMILES database, in this case, has an error and does not add sodium (Na) in its structures for these two chemicals. Although EPIWIN calls these two chemicals as the sodium salts, the estimates do not include sodium in its results. Please note that the

EPIWIN value calculated by the submitter for the dicyclohexyl ester sodium salt is correct (Na is included into the SMILES structure for this chemical).
Health Effects (acute toxicity, repeat dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The test data for sodium bis(1,3-dimethylbutyl) sulfosuccinate and sodium dicyclohexyl sulfosuccinate are sufficient to address endpoints of acute toxicity, repeated-dose toxicity, and reproductive toxicity, provided that the summaries are revised. The IUCLID data will adequately address the potential toxicity of sodium di(2-ethylhexyl) sulfosuccinate, provided that the summaries are revised to include the relevant information to support the conclusions of the submitter. The submitter proposes to use sodium di(2-ethylhexyl) sulfosuccinate data to address the genetic toxicity and developmental toxicity endpoints for the category. The submitter bases this category approach on structural similarity of the esters and "similar toxicological properties." However, the submitter also indicates, in Test Plan Section 2.3, that the alcohol moieties of the esters generate different metabolites. Specifically, the submitter explains that the ethylhexyl alcohol is metabolized to 2-ethylhexanol, while the other two esters in the category are not. The submitter needs to clearly state the toxicological similarities considered and strengthen the discussion of metabolism in the justification for not conducting additional testing.

The evaluations of the specific endpoints provided below assume that additional information will be added to the IUCLID summaries to support the conclusions of the submitter.

Acute Toxicity. Although the study summaries lack critical information, the consistent LD_{50} values for all esters in rats and mice suggest that the data are adequate to characterize the endpoint.

The following error was noted in the Test Plan Section 3.4.1 (page 12), first paragraph: the range for the LD_{50} in mice should be 2.6 - 4.8 g/kg instead of 2.6 - 4.3 g/kg.

Repeated-Dose Toxicity. Out of eight IUCLID summaries submitted for the repeated-dose toxicity endpoint, the key studies were 90-day repeated dose toxicity studies conducted on each sulfosuccinate ester. The available data support the submitter's conclusion that no further testing is required.

Genetic Toxicity Data. Out of four IUCLID summaries submitted for genetic toxicity endpoints, two summaries are adequate for characterization of the genetic toxicity of sodium di(2-ethylhexyl) sulfosuccinate. The submitter proposes using sodium di(2-ethylhexyl) sulfosuccinate as a representative of the category, but has not adequately justified this approach. The submitter needs to clarify the justification by providing a discussion of factors, such as structural alerts or common pathways for metabolism of the compounds, or test one of the other two chemicals to address this endpoint.

Reproductive Toxicity. The existing data are adequate to characterize the reproductive toxicity endpoint. IUCLID summaries were submitted for two three-generation oral reproductive toxicity studies on sodium di(2-ethylhexyl) sulfosuccinate and for 90-day repeated oral exposure studies conducted on all three chemicals. The three-generation studies identified an effect on lactation (possibly taste-aversion to the milk of treated dams) as the most sensitive endpoint in these studies. The submitter concluded that, in contrast to sodium di(2-ethylhexyl) sulfosuccinate, taste aversion was unlikely for the dimethyl ester and sodium dicyclohexyl sulfosuccinate since no effects on weight gain or food consumption were noted at dietary concentrations up to 1.0% in the 90-day studies. The rationale for this statement is unclear because no effects on weight gain or food consumption, suggesting taste aversion in the reproductive study, were noted in the parallel 90-day study of sodium di(2-ethylhexyl) sulfosuccinate. No effects on reproductive organ weights or histopathology were noted in the 90-day studies. The data from the 90-day studies support the conclusion that no further testing is required.

In the Test Plan Section 3.4.5 (page 13), the submitter needs to provide clarification of the following underlined text: "The fact that. . .with palatability (i.e., reduced weight gain in dams and lactation in pups) . . .at this concentration".

Developmental Toxicity. An adequate study (Ref. 13) and supporting data (Ref. 14, 21) are available on the developmental toxicity of sodium di(2-ethylhexyl) sulfosuccinate.

The studies on sodium di(2-ethylhexyl) sulfosuccinate identified adverse developmental effects in rats, which the submitter considered secondary to maternal toxicity. The submitter stated that similar effects could be expected as a result of maternal toxicity in rats exposed to the dimethylbutyl and dicyclohexyl esters at the same dietary concentration. Section 2.3 of the Test Plan states that 2-ethylhexanol, a metabolite of sodium di(2-ethylhexyl) sulfosuccinate in rats, is a developmental toxicant in rats. The submitter needs to explain why it considers the developmental effects secondary to maternal toxicity. EPA believes that the results obtained for sodium di(2-ethylhexyl) sulfosuccinate may not be representative of the other esters unless an additional justification can be provided for use of the category approach for this endpoint or developmental toxicity data are provided for at least one of the other two chemicals.

Ecotoxicity (fish, daphnid and algal toxicity)

Fish. Of the many fish toxicity studies submitted, adequate studies are available, one each for sodium bis(1,3-dimethylbutyl) sulfosuccinate, and sodium dicyclohexyl sulfosuccinate, and three studies for sodium di(2-ethylhexyl) sulfosuccinate; therefore, no further testing is recommended .

Invertebrates. Adequate data are presented for sodium dicyclohexyl sulfosuccinate and sodium di(2-ethylhexyl) sulfosuccinate and no further testing is recommended.

Algae. Adequate data are presented for sodium dicyclohexyl sulfosuccinate. However, EPA disagrees with the submitter that these data address the algal toxicity endpoint for the category. Because sodium di(2-ethylhexyl) sulfosuccinate is more toxic to fish and daphnids than the other two chemicals, and the available algal data on sodium dicyclohexyl sulfosuccinate showed no toxicity, EPA recommends that the submitter conduct a study to characterize the aquatic plant toxicity of sodium di(2-ethylhexyl) sulfosuccinate as potentially the most toxic category member for this endpoint for read-across purposes.

Specific Comments on the Robust Summaries

Health Effects

Acute toxicity. All summaries omitted details of the test protocol used and/or results obtained. Omissions varied by study and included details of dosing, fasting, mortality observed, clinical signs in surviving animals, performance of necropsy, and method of LD_{50} determination.

Genetic toxicity. The study summaries need to include more information on experimental design, including the use of controls, the results obtained, and the method of analysis.

The OECD Test Guideline for the chromosome aberration test on page 19 was incorrectly listed as 471; the correct guideline number is 473.

Reproductive toxicity. The three-generation studies lack the following information: (1) numerical data for all treatment-related responses, including the number of animals evaluated for each endpoint; and (2) the weight of each litter, mean pup weights, and individual pup weights at termination.

Ecotoxicity Studies

In all ecotoxicity robust summaries the submitter needs to clarify the toxicity values that are expressed with “m =” or “c =” (e.g., EC_{50}: c = 457) to indicate whether “m” stands for measured value, and “c” stands for calculated value, because no reference to an SAR model was cited.

Fish. The submitter needs to provide test substance purity information in the robust summary for sodium dicyclohexyl sulfosuccinate, and sodium di(2-ethylhexyl) sulfosuccinate.

Invertebrates. The submitter needs to provide test substance purity information in the robust summary of sodium dicyclohexyl sulfosuccinate and sodium di(2-ethylhexyl) sulfosuccinate.

Algae. The submitter needs to provide information on test substance purity information in the robust summary for sodium dicyclohexyl sulfosuccinate.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.